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Radiotherapy Fractionation for the Palliation of Uncomplicated Painful Bone Metastases

Practice Guideline Report #13-2

JS Wu, R Wong, M Johnston, A Bezjak, T Whelan, N Laetsch, and members of the Supportive Care Guidelines Group

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SUMMARY

Guideline Questions

1. What is the preferred dose-fractionation of localized radiotherapy for the treatment of uncomplicated painful bone metastases?
2. What is the expected response rate and duration of the pain relief?

Target Population

This recommendation applies to adult patients with single or multiple radiographically confirmed bone metastases of any histology corresponding to painful areas in previously non-irradiated areas without pathologic fractures or spinal cord/cauda equina compression. It does not apply to the management of malignant primary bone tumour.

Recommendation

- For patients where the treatment objective is pain relief, a single 8 Gy treatment, prescribed to the appropriate target volume, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases.

Qualifying Statements

- "*Standard*" refers to what is applicable to the majority of patients, with a preference for patient convenience and ease of administration, without compromising treatment efficacy or morbidity.
- The recommendation does not apply to lesions previously irradiated, or lesions causing cord compression or pathologic fractures, because such patients were mostly excluded from clinical trials examining fractionation schedules.
- Prophylactic anti-emetic agents should be considered when a significant proportion of the gastrointestinal tract is in the irradiated volume.
- Patients and referring physicians should be advised that repeat irradiation to the treated area may be possible.
- There is insufficient evidence at this time to make a dose-fractionation recommendation for other treatment indications, such as long term disease control for patients with solitary bone metastasis, prevention/treatment of cord compression, prevention/treatment of pathologic fractures, and treatment of soft tissue masses associated with bony disease.

Methods

A systematic search of the MEDLINE, CANCERLIT, Cochrane Library, and Physician Data Query Clinical Trials databases was performed for the period from 1997 to December 2002. Reference lists and meeting abstracts were scanned for additional citations. Systematic reviews, meta-analyses, or randomized controlled trials comparing two or more dose-fractionation schedules for localized radiotherapy of painful bone metastases were eligible for inclusion in this review of the evidence. Pain relief, quality of life, analgesic consumption, and treatment toxicity were the outcomes of interest.

Evidence was selected and reviewed by four members of the Practice Guidelines Initiative's Supportive Care Guidelines Group. This practice guideline report has been reviewed and approved by the Supportive Care Guidelines Group, which includes palliative care physicians, nurses, radiation oncologists, psychologists, medical oncologists, a chaplain, an anaesthetist, a surgeon, methodologists, and administrators.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. The process consists of periodic review and evaluation of the scientific literature, and, where appropriate, integration of relevant new literature with the original guideline information.

Key Evidence

- Two systematic reviews and 16 randomized controlled trials form the basis of evidence for this practice guideline report.
- Based on intention-to-treat principle, meta-analysis of published data from eight randomized trials of single fraction versus multifraction radiotherapy for the treatment of uncomplicated painful bone metastases did not detect a significant difference in response rate (pain reduction or control) between a single fraction of 8 Gy prescribed to the appropriate target depth and fractionated radiotherapy. Pooled complete response rates were 33% with single fraction and 32% with multifraction (relative risk, 1.03; 95% confidence interval, 0.94 to 1.13, p=0.5) and overall response rates were 62% and 59% respectively (relative risk, 1.05; 95% confidence interval, 1.00 to 1.11, p=0.04).
- The majority of patients enrolled in the studies were breast, prostate, and lung cancer patients. Other less common epithelial and non-epithelial tumours were often included, but relative efficacy of dose-fractionation schedules cannot be determined in such subgroups.
- Median duration of response was 12 to 24 weeks, with no significant difference between fractionation schedules within individual trials.
- No significant difference in quality of life after radiotherapy (in the few studies assessed), analgesic consumption, or acute adverse effects (vomiting and tiredness) was detected between single- and multiple-fractionation schedules.
- Observed re-irradiation rates were higher with single fraction treatment (11-25%) than with multiple-fraction treatment (3-12%). Indications for re-irradiation were not described.
- One study showed greater remineralization following fractionated radiotherapy (30 Gy/10 fractions) than single fraction (8 Gy). The implication of this finding on prevention of pathologic fracture is unclear.

For further information about this practice guideline report, please contact Dr. Rebecca Wong, Co-Chair, Supportive Care Guidelines Group, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, M5G 2M9; TEL 416-946-2919; FAX 416-946-4586; Email: rebecca.wong@rmp.uhn.on.ca

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

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FULL REPORT

I. QUESTIONS

1. What is the preferred dose-fractionation of localized radiotherapy (RT) for the treatment of uncomplicated painful bone metastases?
2. What is the expected response rate and duration of the pain relief?

Outcomes of interest include pain relief (primary outcome), duration of response, quality of life, analgesic consumption, treatment toxicity, re-irradiation rate, pathologic fractures, spinal cord compression, and remineralization.

II. CHOICE OF TOPIC AND RATIONALE

Radiotherapy is a well-recognized, effective modality in the palliative treatment of painful bone metastases. Bone metastases are a common manifestation of distant relapse from many types of malignant tumours, especially from cancers of the lung, breast, and prostate. With the advent of effective systemic therapies and improvements in supportive care, cancer patients are expected to live longer and may suffer from metastatic disease for a considerable length of time. Many patients with bone metastases suffer from compromised mobility and performance status.

The optimal dose-fractionation schedule for the treatment of bone metastases is unclear. Two surveys of Canadian patterns of practice found that various fractionation schedules are employed by radiation oncologists, ranging from a single large-dose fraction (e.g., 8 Gy) to a more prolonged course of 30 Gy/10 fractions over 2 weeks [1;2]. It has been suggested that the choice of fractionation is influenced not only by patient-related factors but also by physician-education and attitudes, treatment toxicity, resource utilization, and departmental policy [3-7]. While different clinicians may associate "*optimal*" with different treatment goals, one could recommend that a "*preferred"* dose-fractionation is one that provides pain relief without undue toxicity and is least onerous to the patient.

During the past decade, significant clinical trial efforts have been devoted to comparing single large-dose radiation (8 Gy to 10 Gy) with multifraction regimens (five to ten fractions) [8-14]. The two largest trials were published in 1999 by the Bone Pain Trial Working Party [10] and the Dutch Bone Metastasis Study group [11]. Results of a Canadian study were presented at the Canadian Association of Radiation Oncologists (CARO) meeting in 2000 and reported in an abstract for the 2000 meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) [9]. These randomized trials should provide substantial evidence to address the question of a "preferred" fractionation for the majority of patients with bone metastases.

This provincial guideline was initiated to summarize the evidence and to provide recommendations on the preferred standard radiotherapy fractionation schedule for the treatment of painful bone metastases.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI), using the Practice Guidelines Development Cycle methodology [15]. Evidence was selected and reviewed by four members of the PGI's Supportive Care Guidelines Group. Members of the Supportive Care Guidelines Group disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the preferred dose-fractionation of radiotherapy for the treatment of uncomplicated painful bone metastases, developed through systematic reviews and evidence synthesis. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. The process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

Two independent literature searches were conducted. The first was a search of PubMed (National Library of Medicine) for the years 1980 to 2000 with no language restrictions, using the search terms “bone”, “metastasis” or “metastases”, "radiation” or “radiotherapy”, and “fraction”. Citations listed in the PubMed output were evaluated for eligibility for the systematic review of the evidence as were those marked “Related” to the eligible papers.

The second search was conducted to complement the results of the search described above. In addition to several randomized controlled trials (RCTs), the original literature search had found five systematic reviews, the most recent of which covered the literature up to August 1998. For this practice guideline report, a second search of MEDLINE, CANCERLIT, and the Cochrane Library (2002, Issue 4) was conducted to find randomized trials published between January 1998 and December 2002 using MeSH headings (radiotherapy, radiotherapy dosage, dose fractionation, bone neoplasms/sc [Secondary], explode Clinical Trials, clinical trial [publication type]), and text words (bon:, osseous, metasta:, radiotherapy, irradiation, radiation, pain, analgesi:, trial, and study) without language restrictions.

Proceedings of the meetings of ASTRO (2001-2002) and the Canadian Association of Radiation Oncologists (2000), as well as reference lists of papers and review articles, were scanned for additional citations. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of ongoing randomized trials. The Canadian Medical Association Infobase (http://www.cma.ca/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) and other web sites were searched for existing evidence-based practice guidelines prior to the development of this guideline report.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met all of the following criteria:

1. They were published reports of either a systematic review of radiotherapy dose-fractionation studies or full or abstract reports of results from RCTs comparing two or more dose-fractionation schedules for localized radiotherapy of painful bone metastases.
2. The article reported data on pain relief for each intervention group.

Exclusion Criteria

Studies of hemi-body radiotherapy or systemic radiotherapy with radionuclides were excluded. Letters and editorials were not considered.

Synthesizing the Evidence

There were some variations in patient population, treatment technique and pain/analgesic scoring method, and measured outcomes among the trials. A summary of these methodologic variations is provided in Appendices 1-3. The studies comparing single against multifraction regimens were the most homogeneous group, and a meta-analysis of these trials was performed based on published response data except for one study, which was reported in

abstract form [9]. Additional data from this study (the Canadian Bone Mets study) was obtained from the investigators by personal communication [16]. No unpublished data was solicited from investigators of other trials.

Pain relief, expressed as a response rate, was the primary outcome for the randomized trials reported here. To estimate the overall effect of radiotherapy on pain relief, complete and/or overall response rates were abstracted from the published reports of individual RCTs and pooled by intention-to-treat using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview © Update Software). For some studies, response rates by intention-to-treat were recalculated using the number of randomized patients as denominator, because these trials did not report response rates by intention-to-treat. Some studies included responses to repeat irradiation in the reported response rates. Pooled response comparisons are expressed as relative risks (also known as risk ratios) with 95% confidence intervals (CI), where a relative risk (RR) for response as the event >1.0 indicates that single fraction radiotherapy improved pain compared with multifraction radiotherapy. Conversely, a relative risk <1.0 suggests that patients in the multifraction group experienced better response to treatment. Sensitivity analysis was done with evaluated patients as the denominators (i.e., not intention-to-treat). An attempt to explore the effect of dose-response, incorporating results from multifraction studies, was done by calculating the biological equivalent doses (BED) for all fractionation schedules using an α/β ratio of 10. Any trial that employed treatment arms above and below a specific BED cut-off was pooled with other trials with similar BED treatment arms. The meta-analysis portion of this practice guideline report has been published [17].

Secondary outcomes evaluated by these trials included analgesic use, quality of life, time to response, duration of response, retreatment with radiotherapy for bone pain, and adverse effects.

IV. RESULTS

Literature Search Results

The literature search identified no evidence-based practice guidelines, five reviews [18-22] and 18 randomized studies [8-14;23-33].

Of the five reviews identified, four were systematic reviews of radiotherapy for painful bone metastases [18-20;22]. The most comprehensive reviews were the Cochrane review by McQuay *et al.* [18], an update of a review first published in 1997 [22], and the review by Ratanatharathorn *et al.* [19]. In both cases, the reviewers concluded that meta-analysis was not appropriate because of variation among studies in patient selection and trial design. The Cochrane Review concluded that no difference in treatment response could be found among various fractionation schedules. In contrast, Ratanatharathorn *et al.* concluded that longer courses of radiation provided improved response. After these reviews were completed, four randomized trials of single versus multifraction RT [9-12], including large studies by the Bone Pain Trial Working Party [10] and the Dutch Bone Metastasis Study group [11], were reported.

Of the 18 randomized trials identified in the literature search, 16 studies form the basis of this review of the evidence (Table 1). Two studies were excluded: one had incomplete accrual and did not report response by treatment arm [8], and the other compared single fraction treatment at multiple dose levels (from 8 Gy to 15 Gy) against multifraction treatment at multiple dose levels (from 20 Gy/5fractions to 30 Gy/6fractions) [33]. A full translation of a paper published in German [12] and a partial translation of one published in Japanese [29] was obtained.

It should be noted that all trials excluded patients previously irradiated (over the site of interest) or with spinal cord compression or pathologic fractures. The exception to the latter eligibility criterion was the RTOG 7402 trial reported by Tong *et al.*, where pathologic fractures were included regardless of prior surgical fixation [32].

All trials included a variety of tumour types, although some were more restrictive than others (Appendix 1). The majority of patients enrolled in these studies were breast, prostate, and lung cancer patients. Other less common epithelial and non-epithelial tumours were often included, but relative efficacy of dose-fractionation schedules cannot be determined in such subgroups. One study excluded patients requiring treatments to the cervical spine [11], while another excluded patients with treatment portals >150 cm^2 over the abdomen/pelvis [14]. Overall, all tumour types appear to be represented, and results should be generalizable.

Depth of dose-prescription varied, but the majority prescribed to a depth of 5 cm when using a single field over the spine (Appendix 1). Maximum entrance dose (at D_{max}) was not described in the published reports.

Repeat radiation treatments were done in a number of trials at the discretion of the treating physician (Table 2). In general, re-irradiation rates were higher with the lower-dose arm of the trials. The possibility of physician-bias towards offering re-irradiation to single fraction patients was discussed by authors of the Bone Pain Trial Working Party and the Dutch study [10;11]. Response rates summarized in the following sections include responses to repeat irradiation, as reported by the trials.

Table 1: Randomized trials of radiotherapy fractionation for painful bone metastases.

Author/Country	Year	Treatment arms (total dose/ # fractions)	# Patients randomized	Included in published systematic reviews [reference numbers]
Trials comparing single fraction against multifraction RT				
Kirkbride *et al.* [9] Canada	2000 (abstract)	- 8 Gy single - 20 Gy/5 fr	398	NI
Bone Pain Trial Working Party [10] UK/New Zealand	1999	- 8 Gy single - 20 Gy/5 fr	765	NI
Steenland *et al*. [11] Holland	1999	- 8 Gy single - 24 Gy/6 fr	1171	NI
Koswig *et al.* [12] Germany	1999	- 8 Gy single - 30 Gy/10 fr	107	NI
Nielsen *et al.* [13] Denmark	1998	- 8 Gy single - 20 Gy/5 fr	241	[18;19]
Gaze *et al.* [14] UK	1997	- 10 Gy single - 22.5 Gy/5 fr	260	[18;19]
Cole [23] UK	1989	- 8 Gy single - 24 Gy/6 fr	29	[18;19]
Price *et al.* [24] UK	1986	- 8 Gy single - 30 Gy/10 fr	288	[18;19]
Trials comparing single fractions at different doses				
Jeremic *et al.* [25] Yugoslavia	1998	4 Gy vs. 6 Gy vs. 8 Gy	327	[19]
Hoskin *et al.* [26] UK	1992	4 Gy vs. 8 Gy	270	[18;19]
Trials comparing different multifraction regimens				
Niewald *et al.* [27] Germany	1996	- 20 Gy/5 fr - 30 Gy/15 fr	100	[18;19]
Rasmusson *et al.* [28] Denmark	1995	- 15 Gy/3 fr - 30 Gy/10 fr	217	[18;19]
Hirokawa *et al.* [29] Japan	1988	- 25 Gy/5 fr - 30 Gy/10 fr	128	[18]
Okawa *et al.* [30] Japan	1988	- 20 Gy/10 fr (BID) - 22.5 Gy/5 fr - 30 Gy/15 fr	80	[18;19]
Madsen [31] Denmark	1983	- 20 Gy/2 fr - 24 Gy/6 fr	57	[18;19]
Tong *et al.* US (RTOG 7402)[32;34]	1982	Solitary metastasis: - 40 Gy/15 fr - 20 Gy/5 fr	266	[18;19]
		Multiple metastases: - 15 Gy/5 fr - 20 Gy/5 fr - 25 Gy/5 fr - 30 Gy/10 fr	750	

Notes: BID – twice daily, fr – fraction(s), Gy – gray, NI – not included, RT – radiotherapy, RTOG – Radiation Therapy Oncology Group

Primary Outcome

Pain Relief

Table 2 summarizes the response rates in terms of complete and partial pain relief. To conform to an intention-to-treat approach, these were calculated by the authors of this practice guideline report from data presented in published reports. Evidence on time to response, duration of pain relief, and rates of re-irradiation of painful sites is summarized in the text below.

Pooled response rates from single 8-10 Gy fraction versus multifraction radiotherapy trials and median duration of response

The complete response rates achieved by a single fraction of 8 Gy or 10 Gy ranged from 9% to 52% across the studies (7 of the 8 studies reported CR), and overall response rates ranged from 21% to 88%. No significant difference was found in pooled complete response rate between single fraction and multifraction radiotherapy (RR, 1.03; 95% CI, 0.94 to 1.14; p=0.5, Figure 1). Overall response rates were slightly higher for single fraction (RR, 1.05; 95% CI, 1.00 to 1.11; p=0.04, Figure 2). The majority of responses were observed within the first two months of treatment [10-13;24]. Only one trial reported a faster response to single fraction radiotherapy (median time-to-response, 5 days) compared to multiple fractions (median time-to-response, 10 days), but no p-value was reported [12].

The results presented above are based on all *randomized patients* (N=3231). Sensitivity analysis using only *evaluable patients* as the denominator showed pooled complete response rates of 39% and 40% for single and multifraction radiotherapy, respectively (RR, 0.97; 95% CI 0.87 to 1.07, p=0.6). The overall response rates were 73% in both groups (RR, 1.00; 95% CI 0.95 to 1.04, p=0.9). Only the Canadian study reported a better "clinically significant response" after 20 Gy/5 fractions than after single fraction treatment, when response rates for evaluable patients were compared (p<0.05) [9].

Median duration of response (for responders only) ranged from 12 to 24 weeks, and there were no significant differences between single and multifraction regimens [10;11;14;24].

Figure 1. Meta-analysis of complete response rates from randomized trials of single versus multiple fractions of radiotherapy for painful bone metastases.

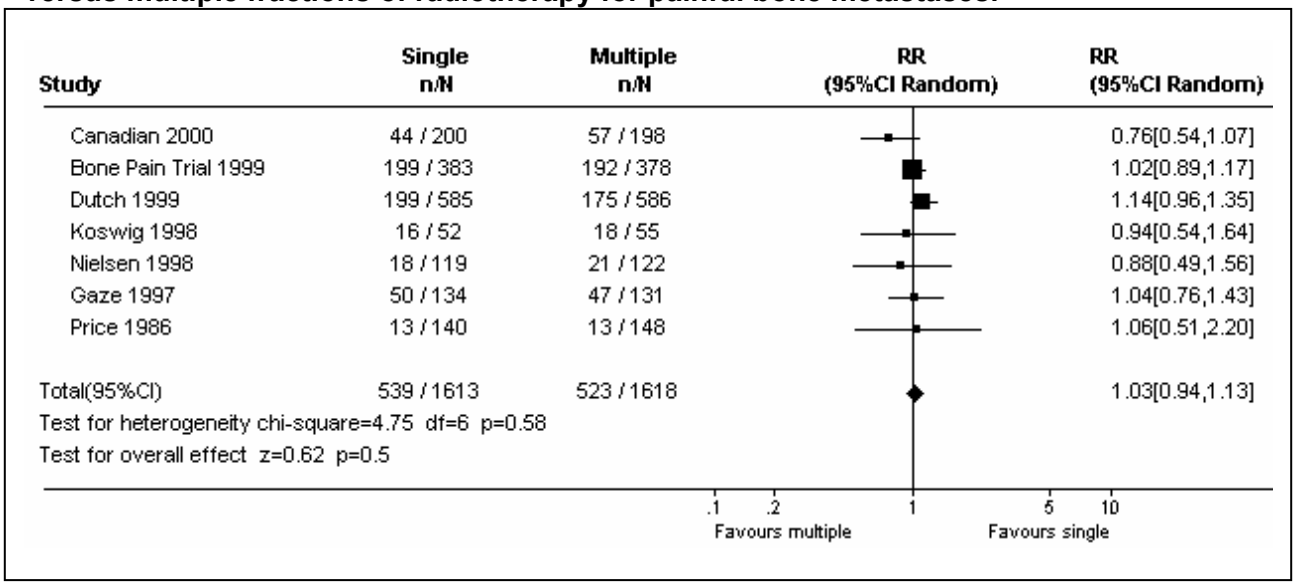
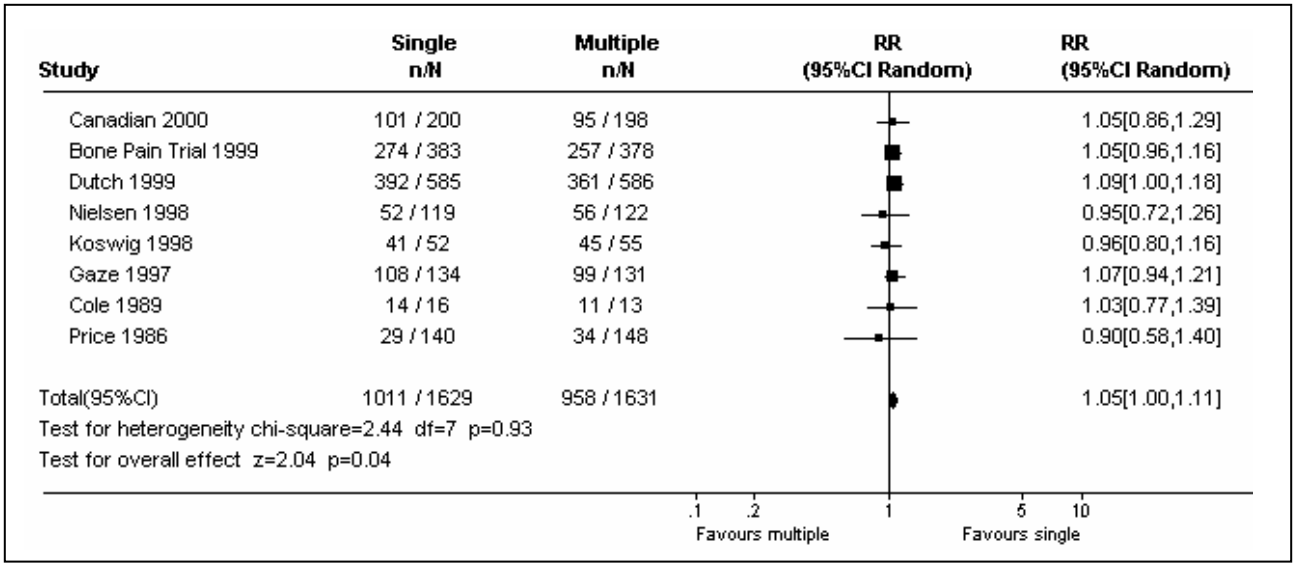


Figure 2. Meta-analysis of overall response rates from randomized trials of single versus multiple fractions of radiotherapy for painful bone metastases.



Response rates and duration for different doses of single fraction radiotherapy

At a single fraction dose of 4 Gy, response rates were lower than those with 8 Gy. Jeremic *et al.* compared doses of 4, 6, and 8 Gy and observed response rates of 59%, 73%, and 78%, respectively. Univariate analysis detected a significant difference between 4 and 8 Gy (p=0.0019) but not between 6 and 8 Gy (p=0.39) [25]. Hoskin *et al.* also detected a significantly higher response rate with 8 Gy (69%) compared to 4 Gy (44%) (p<0.001) [26]. Both Jeremic *et al.* and Hoskin *et al.* reported that pain relief occurred more quickly, an average of a week to 10 days earlier, with 8 Gy than with 4 Gy. This difference was statistically significant in the trial by Hoskin *et al.* (log-rank p<0.01).

The mean duration of response was 42 weeks with 4 Gy and 47 weeks with 8 Gy in the Jeremic *et al*. trial. No difference between doses was detected in duration of response in the Hoskin *et al.* trial. Both authors concluded that single 8 Gy dose is preferred until further studies confirm the equivalence in efficacy at a lower dose such as 6 Gy.

Response rates and duration for different multifraction radiotherapy regimens

For trials comparing different multifraction regimens, no significant difference in response rates among treatments within each study was detected (Table 2). The RTOG 7402 study did find that higher dose-fractionation was associated with a significantly higher complete "combined" pain response rate—defined as both no pain <u>and</u> no analgesic use [34]. No difference was found in complete response that was based on pain score alone. Results favoured higher dose-fractionation for patients with a solitary metastasis and those with multiple metastases. Unfortunately, 45% of patients entered into the solitary-metastasis group were not evaluable primarily due to misclassification [32], and the validity of these results can be challenged. Furthermore, pain was assessed by physicians, who were not blind to treatment allocation, rather than by patients.

Two of five multifraction trials reported significantly earlier onset of pain relief following the shorter fractionation regimens [29;30]. In the trial by Hirokawa *et al.*, the response rate two weeks after treatment was 67% in the group treated with 25 Gy in 5 fractions, compared with 42% in the group treated with 30 Gy in 10 fractions, but the p-value was not reported. Okawa *et al.* reported that responses were observed after a mean of 25 days with 30 Gy/15 fractions

given once a day but took an average of only 12-14 days when radiation was given twice a day for a total dose of 20 Gy/10 fractions ($p<0.05$).

Median duration of response in two multi-fraction trials ranged from 12 weeks [32] to 22 weeks [27, as cited in 19]. There was no significant difference between fractionation regimens as reported. However, in their personal communications with Niewald *et al.* [27], Ratanatharathorn *et al.* [19] found that the median duration of response was 103 days for 20 Gy/5 fractions/one week, versus 155 days for 30 Gy /15 fractions/ three weeks (p values not reported).

Pooled comparisons by Biological Equivalent Dose (BED)

Exploratory analyses, performed by calculating BED using an α/β ratio of 10, did not reveal any difference in response rate at various BED cut-off points. At single fraction doses of 8 Gy or higher, no dose-response relationship could be detected.

Subgroup considerations: patient characteristics associated with response

Subgroup analysis in the Dutch study did not show a difference between single and multifraction in median duration of response (48 weeks) among 92 favourable patients with longer life expectancy. These patients had either breast cancer without visceral metastases and at least one year of disease-free interval, or prostate cancer not yet treated with hormonal therapy [11]. A subgroup of 84 patients with radicular pain in the Bone Pain Trial Working Party did not experience a difference in pain relief between single or multifraction treatments [10]. Lung cancer patients, compared with breast cancer patients, had lower response rates in several studies, irrespective of fractionation schedules [11;25;26;29-32], a finding that was statistically significant in the study reported by Tong *et al.* ($p<0.001$) [32].

Table 2. Response rates (intention-to-treat) and re-irradiation rates.

Study	Complete Response		Any Response		Re-irradiation Rate	
	Low #[1]	High #[2]	Low #	High #	Low #	High #
Trials comparing single fraction against multifraction RT						
Kirkbride *et al.* [9] (abstract)	22%	29%	51%	48%	NR	NR
Bone Pain Trial Working Party [10]	52%	51%	72%	68%	23%	10%
Steenland *et al.* [11]	34%	30%	67%	62%	25%	7%
Koswig *et al.* [12]	31%	33%	79%	82%	NR	NR
Nielsen *et al.* [13]	25%	25%	34%	39%	20%	12%
Gaze *et al.* [14]	37%	47%	81%	76%	NR	NR
Cole [23]	NR	NR	88%	85%	25%	0%
Price *et al.* [24]	9%	9%	21%	23%	11%	3%
Pooled results	**34%**	**33%**	**61%**	**58%**	NR	NR
Trials comparing single fractions at different doses (4Gy vs. 8Gy)						
Jeremic *et al.* [25],	21%	32%	59%	78%	42%	38%
Hoskin *et al.* [26]	36%	39%	44%	69%	20%	9%
Trials comparing different multifraction regimens						
Niewald *et al.* [27]	33%	31%	77%	86%	2%	2%
Rasmusson *et al.* [28]	NR	NR	69%	66%	NR	NR
Hirokawa *et al.* [29]	NR	NR	75%	75%	NR	NR
Okawa *et al.* [30]	37%	41%	78%	76%	NR	NR
Madsen [31]	NR	NR	48%	47%	NR	NR
Tong *et al.* [32;34] (RTOG 7402)						
- Solitary met	53%	61%	82%	85%	24%[4]	11%[4]
- Multiple met	49%[3]	57%[3]	85%	87%	23%[4]	12%[4]

Notes: Gy – gray, met – metastasis(es), NR – not reported, RT – radiotherapy
1 – lower number of fractions for trials of single vs. multiple fractions, lower dose for trials comparing different doses;
2 – higher number of fractions for trials of single vs. multiple fractions, higher dose for trials comparing different doses
3 – 4-arm study for multiple metastases group: 15 Gy vs. 20 Gy vs. 25 Gy vs. 30 Gy. Low # column refers to 15Gy/1week arm; High # column refers to 30 Gy/2weeks arm. P value comparing all 4 arms = 0.26.
4 – Data from Gillick & Goldberg [34]

Secondary Outcomes

Quality of Life

Quality of life data was reported for three randomized trials of single versus multifraction radiotherapy [11;13;14]. There were no statistically significant differences in quality of life scores between single and multiple-fractionation schedules.

Two trials comparing two multifraction regimens measured outcomes related to quality of life. Niewald *et al.* detected no significant difference in mobility score between one-week and three-week courses of daily radiotherapy [27]. Rasmusson *et al.* reported significant improvements from baseline in levels of activity for both fractionation groups (ten fractions versus three fractions) but no difference between treatment groups [28].

Analgesic Consumption

Analgesic consumption was not a primary outcome in any study, although some single fraction trials provided details of trends of consumption before and after radiotherapy [10;13;14]. No significant difference in the pattern of analgesic consumption was observed between treatment arms in these studies, and all consistently showed a trend of reduced analgesic intake following treatment.

Remineralization

The randomized controlled study by Koswig *et al.* reported that remineralization of lytic bone lesions was greater following 30 Gy/10 fractions than after a single treatment with 8 Gy, as determined by CT density measurements [12]. At the six-month follow up, bone density was significantly increased to an average of 173% following 30 Gy/10 fractions, compared to the average of 120% following 8 Gy/one fraction ($p<0.001$).

Adverse Effects

Table 3 summarizes the data available on the acute side effect of vomiting, as well as the rates of pathologic fracture and spinal cord compression. Four trials also assessed tiredness following radiotherapy, and none found a significant difference between treatment regimens [11;13;14;23].

There is no evidence to suggest that fractionated regimens result in fewer cases of acute nausea and vomiting compared with single fraction treatment. Nausea and vomiting are better controlled by prophylactic anti-emetics, as demonstrated in the Canadian study. Complete emesis control was superior with single fraction radiotherapy using prophylactic ondansetron, 8 mg BID x 3 days, compared with 2000 cGy/5 fractions without prophylactic anti-emetic (53% *emesis-free* after single fraction + prophylactic ondansetron versus 35% *emesis-free* for multiple fractionation without prophylaxis) [16]. Vomiting was equally common (30%) in either treatment arm in a subgroup of patients evaluated (n=124) for nausea/vomiting in the Bone Pain Trial study [10].

Table 3. Percentage of patients experiencing adverse effects associated with radiotherapy for painful bone metastases.

Study	Percent with Vomiting		Percent with Pathologic Fractures		Percent with Cord Compression	
	Low[1] #	High[2] #	Low[1] #	High[2] #	Low[1] #	High[2] #
Trials comparing single fraction against multifraction RT						
Bone Pain Trial Working Party [10]	30%[3]	32%[3]	2.0%	0.5%	1.7%	1.1%
Steenland *et al.* [11]	no significant difference		4%	2%	2%	2%
			$p < 0.05$			
Nielsen *et al.* [13]	no significant difference		5%	5%	NR	NR
Cole *et al.* [23]	8%	11%	NR	NR	NR	NR
Price *et al.* [24]	no significant difference		0	1.3%	2.6%	1.3%
Trials comparing single fractions at different doses (4Gy vs. 8Gy)						
Jeremic *et al.* [25]	19%[4]	22%[4]	6%	7%	7%	6%
Trials comparing different multifraction regimens						
Madsen [31]	7%	0	NR	NR	NR	NR
Tong *et al.* [34] (RTOG 7402) - Solitary met - Multiple met	NR NR	NR NR	4% 5%	18% 8%	NR NR	NR NR

Notes: Gy – gray, met – metastasis(es), NR – not reported, RT – radiotherapy, RTOG – Radiation Therapy Oncology Group

1 – lower number of fractions for trials of single vs. multiple fractions, lower dose for trials comparing different doses;

2 – higher number of fractions for trials of single vs. multiple fractions, higher dose for trials comparing different doses;

3 – % of patients experiencing vomiting on days 1-14; subgroup of N =133, recruited into secondary nausea/vomiting study;

4 – RTOG/EORTC grade 1 & 2 nausea/vomiting.

V. INTERPRETIVE SUMMARY

The preferred radiotherapy dose-fractionation schedule for palliation of uncomplicated painful bone metastases has been a controversial subject [19;35-37]. Randomized trials addressing this question are challenged by the heterogeneity of the patient populations, high attrition rates of participants, and the subjective nature of the primary outcome measure, namely that of pain control. In the past decade, pain evaluation has emphasized self-report assessments rather than physician-based scoring [31;38], and this method is well represented among more recently conducted trials [9-14;25;26]. The sophistication of trial design and quality of reporting has also improved considerably during the past decade.

The goal of this systematic review is to enable guideline developers and practitioners to determine whether the available evidence supports the notion of a "standard" dose-fractionation. "*Standard*" refers to what is applicable to the majority of patients, with a preference for patient convenience and ease of administration without compromising treatment efficacy or morbidity. Based on these criteria, a single fraction is a preferred standard if proven efficacious and well tolerated when compared to other fractionation schedules.

Upon examining all reported and completed randomized trials on radiotherapy fractionation for the treatment of painful bone metastases, a number of general observations are evident:

a) Trials comparing a single fraction with multiple fractions are amenable to meta-analysis;

b) Of 16 fractionation trials considered, no one trial has shown convincingly that any one fractionation is superior than another in terms of pain control;
c) In several of the trials, re-treatment to index sites (i.e., repeat radiation) was done at the discretion of the treating physician;
d) Quality of life was not affected by the choice of fractionation.

Our meta-analysis of all published randomized trials found no difference in pain relief between single fraction and multifraction treatments. No increase in acute gastrointestinal morbidity was observed with single fraction treatment compared to multiple fractions, and the Canadian study showed significantly fewer vomiting episodes with single fraction treatment after prophylactic ondansetron was used in cases with treatment fields over the abdomen or pelvis [16]. Based on this information, the authors of this practice guideline concluded that a single fraction at 8 Gy is the preferred standard dose fractionation for patients with *uncomplicated* painful bone metastases.

Anti-emetic agents should be considered as prophylaxis, as in the Canadian study [9], or as treatment of nausea/vomiting following radiotherapy, given that $\geq$ 30% of patients experienced vomiting following single or multifraction treatment in the two studies that specifically collected patient-assessed nausea/vomiting data [9;10].

Single field treatment over the spine should be treated with megavoltage energy to reduce entrance (D_{max}) dose, since in almost all cases the target volume (vertebral body $\pm$ the posterior elements) resides at some depth below the skin.

Some clinicians believe that fractionated regimens of 20 Gy or higher provide a more durable response, especially for patients who have relatively long life expectancies. Available evidence, however, does not support this notion. The subgroup of such “favourable” patients with a median survival of over 18 months showed no difference in complete response rate *or* median response duration when treated with either a single dose of 8 Gy or 24 Gy in 6 fractions in the Dutch study [11].

There is a lack of firm evidence relating fractionation schedule to the prevention of pathologic fracture. No study evaluated the risk of pathologic fracture prior to treatment. Although the pathologic fracture rate was significantly higher after single fraction radiotherapy than after multifraction in the Dutch study [11], the absolute difference was only 2%. The RTOG study, on the other hand, showed a higher fracture rate following high dose fractionation (40 Gy) than low dose treatment (20 Gy) in patients with a solitary metastasis [32]. Therefore, until CT-based bone density measurements [12] are correlated with pathologic fractures, the choice of fractionation for patients at high risk for a pathologic fracture in a weight-bearing bone is unclear, and no evidence-based recommendation can be given. Further studies are required. No study showed a difference between regimens in rates of spinal cord compression following treatment.

It should be noted that the published studies included a heterogeneous group of patients differing in histologies, performance status, severity of pain, extent of disease, and so forth. The fact that breast, prostate, and lung cancer patients constituted the majority of trial patients implies a greater confidence of reproducing treatment results for these patients in practice. However, the evidence does not provide sufficient materials to allow a recommendation based on treatment outcomes among subgroups of different primary tumours or other patient- and tumour-related factors.

Two remaining issues from the trials reviewed require careful consideration. The first is re-irradiation of treated sites. Among the larger single fraction trials, re-irradiation rates were consistently higher at 20-25% following single fraction, compared to 7-12% following multi-fraction regimens [10;11;13]. The real issue here is that re-irradiation was given at the discretion of treating oncologists, who were not blinded to the initial treatment, and no guideline was given to indicate when, why, and what dose of re-irradiation to be given. The probable

physician bias towards re-irradiating single fraction-arm patients was discussed in the Bone Pain Working Party trial and the Dutch study [10;11]. It would be wrong to conclude that the evidence shows that single fraction radiotherapy gives inferior response rates. The evidence *could* suggest a true difference between single fraction and multifraction *might* exist, if response to re-irradiation was excluded from the analysis of the initial treatment. Unfortunately, such data are not available from published reports. From a pragmatic point of view, an additional 10-15% re-irradiation rate given after single fraction, compared with multifraction, still means that the majority of patients can be well palliated with a single fraction of radiotherapy *without* re-treatment.

The second issue is the definition of "response". When response was defined as a reduction in pain intensity accompanied by a reduction in analgesic consumption, two studies showed better response rates with higher doses of radiation [9;34]. However, other studies have reported no such difference [13;14]. The problem associated with differences in response definition and the method of evaluation is discussed elsewhere [39-41]. An International Consensus on Treatment Endpoints following palliative radiotherapy gathered expert opinions on the issue of response definition and concluded that an integrated pain-analgesic approach to measuring pain response is preferred [42]. At present, the available evidence does not lend itself to a pooled comparison of pain response based on this definition.

VI. IMPLICATIONS FOR PRACTICE

While single fraction treatment may be easily adopted as the standard dose fractionation for uncomplicated bone metastases, in day-to-day practice the "optimal" dose fractionation may also be influenced by a combination of patient- and treatment-related factors that require careful consideration and judgement, for example: (a) large treatment volume over the abdomen/pelvis; (b) large lytic metastasis in weight-bearing bone with high risk of pathologic fracture, (c) young patient with relatively long life expectancy, (d) extensive soft tissue mass associated with bone metastases, (e) site(s) previously irradiated requiring consideration of repeat radiation. None of these patient/treatment factors alone is an absolute contra-indication to single fraction radiotherapy but what guidance does the evidence provide in such scenarios?

a) Large treatment portals over the abdomen/pelvis

The evidence reviewed does not specifically address the results of large volume (i.e. wide-field, hemi-body irradiation), single fraction treatment. Although average treatment volumes were not reported in any of the single fraction trials, a significant proportion of patients did receive treatments to the lumbar spine and pelvis [10;11;13;16]. Since treatment volume was not an inclusion or exclusion criterion among these studies, it is reasonable to assume that study patients represent the majority of treatment volumes treated in an average department. No difference in nausea and vomiting was seen in the subgroup of 133 patients from the Bone Pain Trial Working Party study, who were asked to self-assess nausea/vomiting experience in the first 14 days following treatments [10]. Therefore, the evidence does not support the choice of fractionated treatment based on volume consideration. However, the use of prophylactic ondansetron was shown to significantly reduce vomiting episodes in the single fraction arm compared with the 20 Gy arm (no prophylactic ondansetron) in the Canadian Bone Mets study [16]. For treatment over the epigastrium or lumbar spine, or with larger treatment volumes in the pelvis, it is reasonable to use a prophylactic anti-emetic, as one would for hemi-body irradiation. Patients may also be instructed to use anti-diarrheal agents if enteritis is experienced.

b) Risk of pathologic fracture

Since none of the randomized trials included a systematic fracture-risk assessment prior to treatments, no evidence-based recommendation related to fracture risk can be made.

Patients at risk of pathologic fractures in long or weight-bearing bones should be assessed by an orthopaedic surgeon. Where radiotherapy is considered for tumour downsizing prior to an orthopaedic procedure, or for such patients who are not surgical candidates, fractionated treatment (e.g., 20 Gy/5#, 30 Gy/10#) would be considered appropriate by many clinicians. A discussion of fracture risk assessment is beyond the scope of this review but has been published elsewhere [43-45].

c) Young patient with long life expectancy
The underlying concern for this group of patients is whether single large-dose radiation compromises subsequent tolerance to re-irradiation. Although no untoward late effects were reported by the single fraction studies with follow-up of one year or more [10;11], clinicians may be uneasy about the long-term effects of repeated radiation. Given the lack of evidence to the contrary, single fraction radiotherapy remains an appropriate treatment option in this subgroup.

d) Soft tissue mass associated with bone metastases
With CT/MRI diagnostic investigations becoming more routinely available, and the introduction of the CT-simulator into many departments, the extent of metastatic disease is likely to be better evaluated than in the past. In cases where lytic disease is associated with a large soft tissue mass (e.g., in the acetabulum and adjacent pelvic bone), the desired palliative endpoint may be tumour shrinkage as well as pain control. No evidence-based recommendation can be given for this scenario.

e) Indications for re-irradiation and dose
Re-irradiation may be considered in three scenarios: 1) no pain relief or pain progression after initial radiotherapy, 2) partial response with initial radiotherapy and the hope of achieving further pain reduction with more radiotherapy, and 3) partial or complete response with initial radiotherapy but subsequent recurrence of pain. Response after re-irradiation may be different for each of these scenarios. Only two studies reported response rates to re-irradiation [46;47] with doses ranging from 4Gy as a single dose to 30 Gy/10fractions/2-weeks. At present <u>no</u> clear guideline can be given regarding dose fractionation of re-irradiation and further studies are needed.

VII. ONGOING TRIALS

Further analysis of analgesic consumption and quality of life data are pending from the completed Dutch study [11].

The Supportive Care Guidelines Group is aware of two relevant on-going randomized trials. The Trans-Tasman Radiation Oncology Group study (TROG 96.05) compares responses to single fraction (8 Gy) against multifraction (20 Gy/5 fractions) radiotherapy in patients with neuropathic bone pain. An interim analysis has been published [8] but no analysis by treatment group is available. The Radiation Therapy Oncology Group is conducting a randomized trial (RTOG 9714) comparing a single fraction of 8 Gy against 30 Gy given in 10 fractions over two weeks in patients with breast and prostate cancer who have the expectation of relatively long survival. This trial will provide more data on combined pain-analgesic response and durability of response, as well as the impact of radiotherapy on quality of life [48].

VIII. SUPPORTIVE CARE GUIDELINES GROUP CONSENSUS PROCESS

The Supportive Care Guidelines Group discussed the first draft of this practice guideline report in March 2001. They agreed that a review of the evidence suggested that there was no real difference in response between a single fraction and multiple fractions of radiation. The group discussed the inclusion of the Canadian study that had been published only in abstract

form [9] and concluded that it would be appropriate to include it because it contributed to the overall picture. They also debated the merits of including the three, non-English papers reporting RCTS that were found by the literature search [12;29;33]. It was pointed out that, without a search of databases likely to include the bulk of the non-English literature, these may constitute a biased sample of that subset of the evidence. Translations of these papers were available, and a decision was made to include them. The final issue discussed concerned whether or not data from the randomized trials should be pooled in a meta-analysis. The Cochrane review group had decided not to pool response rates for their systematic review because of some variation among studies in definitions of response and the difficulties with inclusion of systemic radiotherapy trials [18]. However, the Supportive Care Guidelines Group felt that these differences were not substantial enough to preclude pooling the group of studies that compared single fraction with multifraction localized radiotherapy. Since some of the studies reported outcomes including response to re-irradiation, the role of re-irradiation should be considered when applying results of study patients to general radiation oncology practice.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendation

Based on the evidence described above, the Supportive Care Guidelines Group drafted the following recommendation:

Target Population

The recommendation applies to adult patients with single or multiple radiographically confirmed bone metastases corresponding to painful areas, without pathologic fractures or spinal cord/cauda equina compression, for malignant primary tumours of any histology in previously non-irradiated areas of the body.

Draft Recommendation

Key Recommendation

- A single 8 Gy treatment, prescribed to the appropriate depth, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases.

Qualifying Statements

- The recommendation does not apply to lesions in the skull, hands or feet, or to lesions causing cord compression or pathologic fractures.
- Prophylactic anti-emetic agents should be considered when a significant proportion of the gastrointestinal tract is in the irradiated volume.
- Patients and referring physicians should be advised that repeat irradiation to the treated area may be possible.
- Weight bearing bones that appear to be at higher risk of pathologic fracture may require assessment by an orthopaedic surgeon and may be considered for fractionated treatments.

Practitioner Feedback

Based on the evidence and draft recommendation presented above, feedback was sought from Ontario radiation oncologists.

Methods

Practitioner feedback was obtained through a mailed survey of 95 radiation oncologists across Ontario. The survey consisted of items evaluating the methods, results, and interpretive

summary used to inform the draft recommendation and whether the draft recommendation above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 9, 2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Supportive Care Guidelines Group reviewed the results of the survey.

Results

Key results of the practitioner feedback survey are summarized in Table 4. Fifty-nine of the 95 surveys were returned (62% return rate). Fifty-one respondents (86%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice, and three left that question blank but completed the rest of the survey. A total of 54 practitioners (57%) completed the survey.

Table 4. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (% responders to survey*)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	53 (98)	0	1 (2)
There is a need for a clinical practice guideline on this topic.	46 (85)	7 (13)	1 (2)
The literature search is relevant and complete.	51 (94)	3 (6)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	44 (83)	5 (9)	4 (8)
The draft recommendations in this report are clear.	48 (91)	4 (8)	1 (2)
I agree with the draft recommendations as stated.	39 (74)	5 (9)	9 (17)
This report should be approved as a practice guideline.	39 (75)	5 (10)	8 (15)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice*?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	42 (78)	6 (11)	6 (11)

* may not equal 100 percent due to rounding error

Summary of Written Comments

Twenty-one respondents (42%) provided written comments. Several practitioners commented that the guideline was very well done and reflected their current practice. The main points contained in the written comments were:

1. Two practitioners questioned the rationale for excluding lesions to the skull, hands, and feet from the recommendation. One practitioner also questioned the evidence for fractionated treatment for weight-bearing bones at risk of pathologic fracture.

2. A request was made to define the term "standard" in the Key Recommendation section of the summary.

3. Two practitioners commented that there is no mention of the energy of the radiation beam employed or the maximum entrance dose in the guideline report.

4. Two practitioners suggested that the single 8 Gy treatment recommendation be prescribed to the target *volume* rather than the appropriate *depth* to reflect modern prescription

practice. One of these practitioners also felt that the qualifying statement regarding the risk of pathologic fractures also needed clarification since the guideline report suggests that there is insufficient evidence on which to base a recommendation.

5. One practitioner commented that some histologies such as sarcoma and melanoma are underrepresented in the trials included and that the recommendations be revised so that they apply to patients with metastatic non-small cell lung cancer, breast, and prostate cancer.

6. One practitioner suggested rewording the Key Recommendation to reflect the heterogeneity that exists among patients with bone metastases and the need to consider other aspects of patient care and symptom control in addition to local pain.

7. One practitioner noted that the report does not comment on the sensitizing effect of certain chemotherapy agents (e.g., taxanes).

8. One practitioner commented that the guideline is unlikely to improve patient care since patient care outcomes were the same. The practitioner noted that the only danger is that the guideline will be too widely applied. A few practitioners commented that there is insufficient evidence in the guideline report for the stated recommendation. One suggested the recently closed RTOG 9714 study would provide key information. Another practitioner commented that a trial based in his/her centre demonstrated a benefit for prolonged fractionation and that he/she would not change his/her practice based on this guideline report. Another practitioner emphasized that the trials on which the recommendation is based did not properly assess prevention of recurrence of pain or prevention of collapse or fracture of bone. This practitioner felt that lack of evidence that fractionation is superior to single dose was not sufficient to draft the recommendation. Finally, one practitioner commented that the report does not reflect the likelihood that patients in early stages of systemic disease may be harmed by a single fraction.

Modifications/Actions

1. The qualifying statement that the recommendation does not apply to lesions in the skull, hands, or feet was removed because none of the reviewed trials reported the inclusion or exclusion of these anatomic sites from the trials. The choice of fractionation in these sites should respect the volume of normal tissues (especially, brain) included.

2. The word “standard” explained in the Interpretive Summary of the full report was added to the Qualifying Statements section of the summary and full report.

3. Statements were added to the Results and Interpretive Summary sections commenting on choice of energy for single fraction. The authors decided not to provide a recommendation in terms of maximum entrance dose since this information was not reported in the included studies.

4. The Key Recommendation was revised as suggested such that a single 8 Gy treatment is prescribed to the target volume. Another qualifying statement was added to explain that there is insufficient evidence to make a dose-fractionation recommendation for various other indications outside the scope of this report, including prevention of pathologic fractures. Under Implications for Practice, the paragraph on risk of pathologic fractures was revised but no firm recommendations can be made.

5. A paragraph was added to the Key Evidence section indicating that the majority of patients had breast, prostate, or lung cancer. A similar statement was added to the Results section of the full report.

6. The Key Recommendation was revised to reflect the practitioner's comment. The recommendation currently applies to patients for whom the treatment objective is pain relief.

7. No study reported any potential interaction between radiation and chemotherapeutic agents for the patients studied. The significance of such interaction in the context of bone metastases palliative radiotherapy is unknown.

8. The guideline authors considered these comments and maintain their recommendations. No changes were made to the document in response to these comments. The RTOG 9714 trial is listed in the Ongoing Trials section of this report. New information will be added as it becomes available.

Practice Guideline Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eleven of fourteen members of the PGCC completed and returned ballots. Ten PGCC members approved the practice guideline report as written and one member approved the guideline and provided suggestions for consideration by the Supportive Care Guidelines Group. Suggestions made were to reword the target population section and to clarify the second qualifying statement.

Modifications/Actions

The Supportive Care Guidelines Group agreed with the suggestions and modified the target population section and the second qualifying statement accordingly.

X. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Supportive Care Guidelines Group and the PGCC.

Target Population

This recommendation applies to adult patients with single or multiple radiographically confirmed bone metastases of any histology corresponding to painful areas in previously non-irradiated areas without pathologic fractures or spinal cord/cauda equina compression. It does not apply to the management of malignant primary bone tumour.

Recommendations

- For patients where the treatment objective is pain relief, a single 8 Gy treatment, prescribed to the appropriate target volume, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases.

Qualifying Statements

- "*Standard*" refers to what is applicable to the majority of patients, with a preference for patient convenience and ease of administration, without compromising treatment efficacy or morbidity.
- The recommendation does not apply to lesions previously irradiated, or lesions causing cord compression or pathologic fractures, because such patients were mostly excluded from clinical trials examining fractionation schedules.

- Prophylactic anti-emetic agents should be considered when a significant proportion of the gastrointestinal tract is in the irradiated volume.
- Patients and referring physicians should be advised that repeat irradiation to the treated area may be possible.
- There is insufficient evidence at this time to make a dose-fractionation recommendation for other treatment indications, such as long term disease control for patients with solitary bone metastasis, prevention/treatment of cord compression, prevention/treatment of pathologic fractures, and treatment of soft tissue masses associated with bony disease.

XI. JOURNAL REFERENCE

Wu JS, Wong RKS, Lloyd NS, Johnston M, Bezjak A, Whelan T; Supportive Care Guidelines Group of Cancer Care Ontario. Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases - an evidence-based practice guideline. BMC Cancer. 2004;4:71.

XII. ACKNOWLEDGMENTS

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For a complete list of Supportive Care Guidelines Group members and the Practice Guidelines Coordinating Committee, please visit our web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1: Patient entry criteria and depth of dose prescription in randomized trials of radiotherapy fractionation for painful bone metastases.

Study	Entry Criteria		Prescription Point (spine)
	Primary Site	Life Expectancy	
Trials comparing single fraction against multifraction RT			
Kirkbride *et al.* [9]	Breast, prostate, lung, bladder, kidney	>4 months	Cervical-spine = 4cm Thoracic-spine = 3cm Lumbo-sacral spine=5cm
Bone Pain Trial Working Party [10]	Any	No restriction	5 cm
Steenland *et al.* [11]	Solid tumours except renal cell & melanoma	Not discussed*	Not specified
Nielsen *et al.* [13]	Any	>6 weeks	Maximum absorbed dose
Koswig *et al.* [12]	Breast, lung, prostate, kidney	*Not discussed**	Not specified
Gaze *et al.* [14]	Any epithelial	*>4 weeks*	"to the appropriate depth"
Cole [23]	Any	Not discussed*	"applied dose"
Price *et al.* [24]	Any	>6 weeks	5 cm
Trials comparing single fractions at different doses			
Jeremic *et al.* [25]	Any	> 8 weeks	5 cm
Hoskin *et al.* [26]	Any	>6 weeks	5 cm
Trials comparing different multifraction regimens			
Niewald *et al.* [27]	Any	Not discussed*	Reference point within target volume
Rasmusson *et al.* [28]	Breast only	Not discussed*	At depth but ≤7 cm
Hirokawa *et al.* [29]	Any	Not discussed*	Not specified
Okawa *et al.* [30]	Any	Not discussed*	Not specified
Madsen [31]	Any	Not discussed*	Thoracic-spine= 5 cm Lumbar-spine= 7 cm
Tong *et al.* [32] (RTOG 7402)	Any	>3 months	Not specified

* no eligibility criterion related to life expectancy reported

Appendix 2: Primary outcome evaluation in randomized trials of radiotherapy fractionation for painful bone metastases.

Study	Pain Scale	Pain Assessed by	Definition of Complete Response	Definition of Response
Trials comparing single fraction against multifraction RT				
Kirkbride *et al.* [9]	0 to 5 (McGill-Melzack)	Patient	↓pain score with ↓analgesics OR pain score=0 without ↑analgesics, at 3 months	not reported
Bone Pain Trial Working Party [10]	none, a little, quite a bit, very much	Patient	no pain	↓pain score
Steenland *et al.* [11]	11-point scale: 0 (no pain) to 10 (worst imaginable pain)	Patient	pain score of 0 or 1	↓pain score by ≥2 points
Koswig *et al.* [12]	none, mild, moderate, severe	Patient	no pain	not defined
Nielsen *et al.* [13]	none, mild, moderate, severe, excruciating + Visual Analogue scale	Patient	no pain	↓≥50% in VAS score OR ↓ ≥1 category on 5-point scale
Gaze *et al.* [14]	completely pain free, mild discomfort, moderate pain, severe pain, intractable pain	Patient & physician	no pain	↓pain score by ≥1 category
Cole [23]	5-point scale	Patient & physician	outcome not assessed	↓pain score by ≥1 category
Price *et al.* [24]	none, mild, moderate, severe	Patient	no pain	↓pain score by ≥1 category
Trials comparing single fractions at different doses				
Jeremic *et al.*[25]	none, mild, moderate, severe	Patient	no pain	↓pain score by ≥1 category
Hoskin *et al.* [26]	none, mild, moderate, severe	Patient	no pain	↓pain score by ≥1 category
Trials comparing different multifraction regimens				
Niewald *et al.*[27]	none, slight, moderate, severe	Patient	no pain	↓pain score by ≥1 category
Rasmusson *et al.* [28]	none, slight, moderate, severe	Patient & physician	not reported	not reported
Hirokawa *et al.* [29]	none, mild, moderate, severe	Patient	not clear	not clear
Okawa *et al.* [30]	none, mild, moderate, severe, unendurable	Not stated	no pain	↓pain score by ≥1 category
Madsen [31]	visual analogue scale with anchors no pain and unendurable	Patient	not reported	↓analgesic consumption without ↑pain score OR ↓pain score by ≥1 category without ↑analgesic consumption
Tong *et al.* [32] (RTOG 7402)	none, mild, moderate, severe	Not stated	no pain	↓pain score (severity X frequency)

Appendix 3: Other outcomes evaluated in randomized trials of radiotherapy fractionation for painful bone metastases.

Study	Analgesic Use	Quality of Life	Time to Response	Duration of Response	Other
Trials comparing single fraction against multifraction RT					
Kirkbride *et al.* [9]	Y	-	-	-	- complete emesis control
Bone Pain Trial Working Party [10]	Y	-	Y	Y	- retreatment
Steenland *et al.* [11]	Y	Y	Y	Y	- retreatment - fractures & spinal cord compression
Nielsen *et al.* [13]	Y	Y	Y	Y	- retreatment
Koswig *et al.* [12]	Y	-	Y	-	- recalcification
Gaze *et al.* [14]	Y	Y	-	-	- anxiety and depression
Cole [23]	-	-	-	-	- Karnofsky performance status
Price *et al.* [24]	Y	-	Y	Y	-
Trials comparing single fractions at different doses					
Jeremic *et al.* [25]	Y		Y	Y	- retreatment - fractures & spinal cord compression
Hoskin *et al.* [26]	Y	-	Y	Y	-
Trials comparing different multifraction regimens					
Niewald *et al.* [27]	-	-	Y	Y	- mobility - retreatment - recalcification
Rasmusson *et al.* [28]	Y	-	-	-	- radiologic response
Hirokawa *et al.* [29]	-	-	-	-	-
Okawa *et al.* [30]	-	-	Y	-	-
Madsen [31]	Y	-	-	-	-
Tong *et al.* [32] (RTOG 7402)			Y	Y	- retreatment - fractures